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NEW FUNCTIONALIZED POLYMERIC REAGENTS

TECHNICAL FIELD

The present invention relates to polymer supports useful in solution and solid-phase synthesis. It relates more specifically to functionalized polymeric reagents, comprising an acid labile isonitrile moiety. In further aspects the present invention also relates to use of such functionalized polymeric reagents in solution and solid-phase synthesis, a method for preparing an organic compound by solution or solid-phase synthesis using such functionalized polymeric reagents, a method for preparing such functionalized polymeric reagents and to kits comprising the functionalized polymeric reagenta according to the invention. The present invention also relates to new intermediates for use in the preparation of the novel functionalized polymeric reagents.

BACKGROUND ART

The use of solid-phase synthesis for the synthesis of organic compounds has received a lot of attention lately. The reason for this is that solid-phase synthesis has several advantages compared to traditional solution-phase synthesis. Examples of such advantages include the ease with which products can be separated and purified from excess reagents by a simple washing step and the rapid isolation of product when cleaved and washed from the polymeric support.

The concomittant evolution of combinatorial chemistry and the improvement in automated syntheses has put a bonus on functionalized polymeric reagent. Combinatorial chemistry, combined with High Throughput Screening has revolutionized the speed with which the pharmaceutical industry can produce and screen compounds.

A prerequisite for solid-phase synthesis is a functionalized and stable polymeric support. Many of the commercially available polymeric supports have been developed for solid-

phase peptide synthesis and are therefore not inevitably suitable for solid-phase synthesis of compounds with non-peptidic structures.

Although highly successful, solid-phase synthesis exhibits several shortcomings due to the nature of heterogeneous reaction conditions, of which non-linear kinetic behavior is one. By replacing insoluble polymers, such as cross-linked polystyrene, with soluble polymers, such as PEG, the familiar reaction conditions of classical organic chemistry is reinstated, and yet product purification is still facilitated through application of macromolecular properties. This methodology in essence avoids the difficulties of solid-phase synthesis while preserving its positive aspects.

A key step in the synthesis of libraries of non-peptidic structures, or other biological active compounds in general, is to find the shortest synthetic pathway in order to speed up the chemistry optimization and production phase. One alternative is to use multicomponent reactions involving at least 3 reactants, which directly gives the product in a very efficient process. Several multicomponent reactions (MCR) have been described in the literature and one of the most widely utilized is the Ugi MCR. Multicomponent reactions can be performed either in solution or on solid phase. Although the solution phase alternative has proven its efficiency for the synthesis of a large number of biological compound, its major drawback is the need of purification steps in order to remove the excess of starting materials. This slows down the overall production process and/or limits its appropriateness for automated or semi-automated synthesis.

One commercially available functionalized polymeric reagent comprising an isonitrile moiety is shown below in Figure 1. The isonitrile moiety can not be cleaved from the polymeric support by acid treatment.

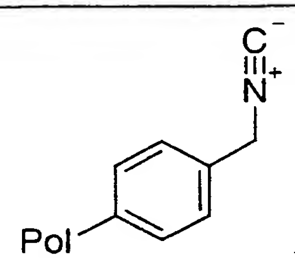


Figure 1. Commercially available functionalized polymeric reagent containing an isonitrile moiety

This drawback is overcome by the present invention, which thereby introduces a novel use for functionalized polymeric reagents comprisingan isonitrile moiety. Isonitriles have always been a poor source of diversity in combinatorial chemistry. This is due to the low number of commercially available isonitriles and the cost associated with time-consuming efforts of custom syntheses of a large number of diverse isonitriles. The present invention overcomes these problems by use of a resin capture strategy where the reactive isonitrile moiety is attached to the polymeric support in such a way as to make it cleavable by acid. The resin capture strategy used has a further advantage in that it gives no by-products that are fragments of the desired final product. Compounds synthesized by this resin capture strategy and released by acid cleavage are pure and do not require any further purification steps.

SUMMARY OF THE INVENTION

The present invention provides a functionalized polymeric reagent comprising a linker moiety for use in solution and solid-phase synthesis. The linker is compatible with a number of reagents and reaction conditions used in the synthesis of organic compounds. The functionalized polymeric reagent is also useful in combinatorial chemistry.

Thus, one aspect of the present invention is a functionalized polymeric reagent for use in solution and solid-phase synthesis. The functionalized polymeric reagent comprises a

linker, and said linker comprises an acid labile isonitrile moiety. The linker is covalently attached to the polymeric support.

In another aspect the present invention provides a method for preparing an organic compound by solution or solid-phase synthesis. The method comprises the step of immobilizing a substrate compound on the polymeric support via said isonitrile moiety. The thereby attached substrate compound is thereafter taken through at least one further organic reaction step to produce the desired compound, which is thereafter cleaved from the polymeric support and isolated. In a preferred embodiment, said method is performed with a variegated population of substrates and/or a plurality of organic reactions to provide a library of organic compounds.

In another aspect the present invention provides a method for preparing an organic compound by solution or solid-phase synthesis. The method comprises the step of a multi-component reaction being performed on the acid labile isonitril moiety of the functionalized polymeric reagent. In a preferred embodiment the multi-component reaction is an Ugi or an Ugi-type reaction.

In another aspect the present invention provides a method for preparing a functionalized polymeric reagent. The method comprises the step of reacting a suitable polymeric support comprising an amino group with a "formylating" reagent. The thereby produced formamido group is thereafter converted to an isonitrile moiety. In a preferred embodiment the amino group is treated with 2,4,5-trichlorophenylformate in DMF and the resulting formamido group is treated with triphenylphosphine / carbon tetrachloride and triethylamine in dichloromethane.

In another aspect the present invention provides new intermediates for use in the preparation of the novel functionalized polymeric reagents.

Accordingly, it is an object of the present invention to provide a functionalized polymeric reagent for use in solution or solid-phase synthesis.

It is another object of the present invention to provide a method for preparing an organic compound by solution or solid-phase synthesis.

It is another object of the present invention to provide a method for preparing a library of organic compounds.

It is another object of the present invention to provide a method for preparing a functionalized polymeric reagent.

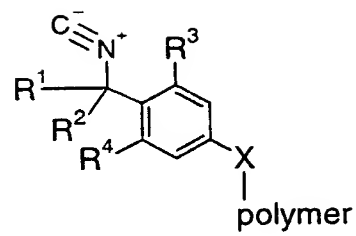
It is another object of the present invention to provide a new intermediate for use in the preparation of a functionalized polymeric reagent.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to functionalized polymeric reagents suitable for solution and solid-phase synthesis, to preparation of said functionalized polymeric reagents, and to use of said functionalized polymeric reagents in solution and solid-phase synthesis of organic compounds, including libraries.

In one aspect, the present invention provides a functionalized polymeric reagent for use in solution and solid-phase synthesis. The functionalized polymeric reagent comprises a polymeric support and an acid labile isonitrile moiety , wherein said polymeric support comprises a polymer and a linker. The linker is covalently attached to the polymer and the isonitrile moiety is covalently attached to the linker.

Preferred functionalized polymeric reagents of the present invention are those of Formula I



(I)

wherein

X is oxygen, a PEG-chain or a $-(CH_2)_n$-CONH- group,

R^1 is carbon, hydrogen, phenyl, or substituted phenyl group,

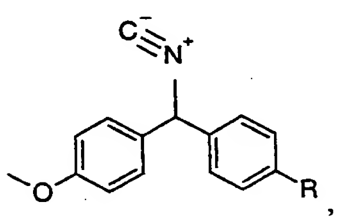
R^2 is hydrogen, phenyl, or substituted phenyl group

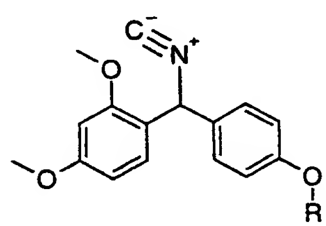
R^3 is hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or phenoxy,

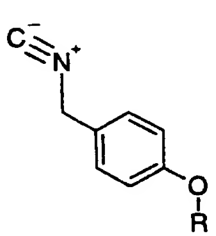
R^4 is hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or phenoxy, and

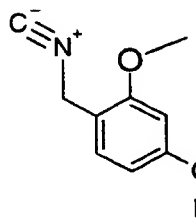
n is an integer from 1 to 4.

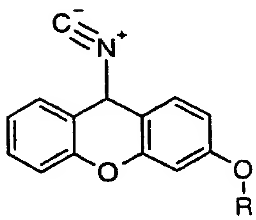
More preferred functionalized polymeric reagents of the present invention are

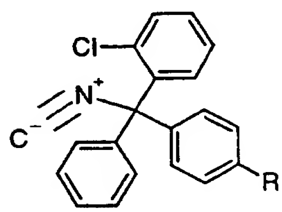












wherein R is a polymer directly attached to the linker or through a PEG-chain or a –$(CH_2)_n$-CONH- group.

The following definitions shall apply throughout the specification and the appended claims:

The term " functionalized polymeric reagent" denotes a reagent that is covalently attached to a linker moiety, and said linker is covalently attached to a polymer.
The term “polymeric support” denotes a polymer covalently attached to a linker moiety, which can optionally further be attached to a substrate compound.
The term "linker" denotes a reactive functional group that can be used to link molecules onto polymeric supports.
The term "acid labile isonitrile" denotes an isonitrile moiety which is cleaved from the linker when treated with aqueous trifluoroacetic acid (95%) at room temperature with a half time of less than 30 minutes.
The term "substrate compound" denotes a compound to be modified in a subsequent reaction step.

The term "immobilize" denotes the act of linking, *e.g.* a substrate compound, by means of chemical or biological procedure to a polymeric support.

The term "multicomponent reaction" denotes a one-pot reaction that form products from at least three different starting materials and incorporate substantial portions of these reagents into the product. This includes reactions involving at lest three different functional groups, some of which may be parts of the same reagent molecule.

The term "variegated population" denotes a population including at least two different chemical entities, e.g., of different chemical structure. For example, a "variegated population" of nucleophiles would comprise at least two different nucleophiles.

The term "substituted phenyl" denotes a phenyl group substituted with at least one of the following; C_1-C_6 alkyl, C_1-C_6 alkoxy, halogen, or phenoxy group.

The term "formylating reagent" denotes a reagent that can convert an amino group into a formamido group.

Polymeric supports

The choice of the soluble or insoluble polymer of the polymeric support is not crucial. Suitable soluble and insoluble polymers therefore consists of those known to the skilled artisan in the art of solution or solid-phase synthesis. Examples of suitable insoluble polymer include, but is not limited to, inorganic substrates, *e.g.* kieselguhr, silica gel and controlled pore glass. and polymeric organic substrates, *e.g.* polystyrene, polypropylene, polyethylene glycol, , as well as composite inorganic/polymeric substrates such as polyacrylamide supported within a matrix of kieselguhr particles. Preferred insoluble polymers are 1% DVB polystyrene and polystyrene-PEG.

Examples of suitable soluble polymers include, but is not limited to, polystyrene (not cross-linked, polyvinyl alcohol, polyethylene imine, polyacrylic acid, polymethylene oxide, PEG, polypropylene oxide, cellulose, polyacrylamide, PEG with 3,5-diisocyanatobenzyl chloride, PEG with 3-nitro-3-azapentane 1,5-diisocyanate, polyvinyl

alcohol-poly(1-vinyl-2-pyrrolidinone, polystyrene-poly(vinyl-substituted monosaccharides), poly(N-isopropylacrylamide)-poly(acrylic acid derivatives).

By replacing insoluble polymers with soluble polymers the familiar reaction conditions of classical organic chemistry is reinstated, and yet product purification is still facilitated through application of macromolecular properties. The present invention thereby avoids the difficulties of solid-phase synthesis while preserving its positive aspects.

Linkers

The choice of the linker is not limited to MAMP resin (amino-(4-methoxyphenyl)methyl polystyrene) (A), and therefore also includes, but is not limited to, Rink amide (B), Wang amino (C), Sasrin amino (D), Sieber amide (E) and 2-chlorotrityl linker (F) shown in Figure 2 below.

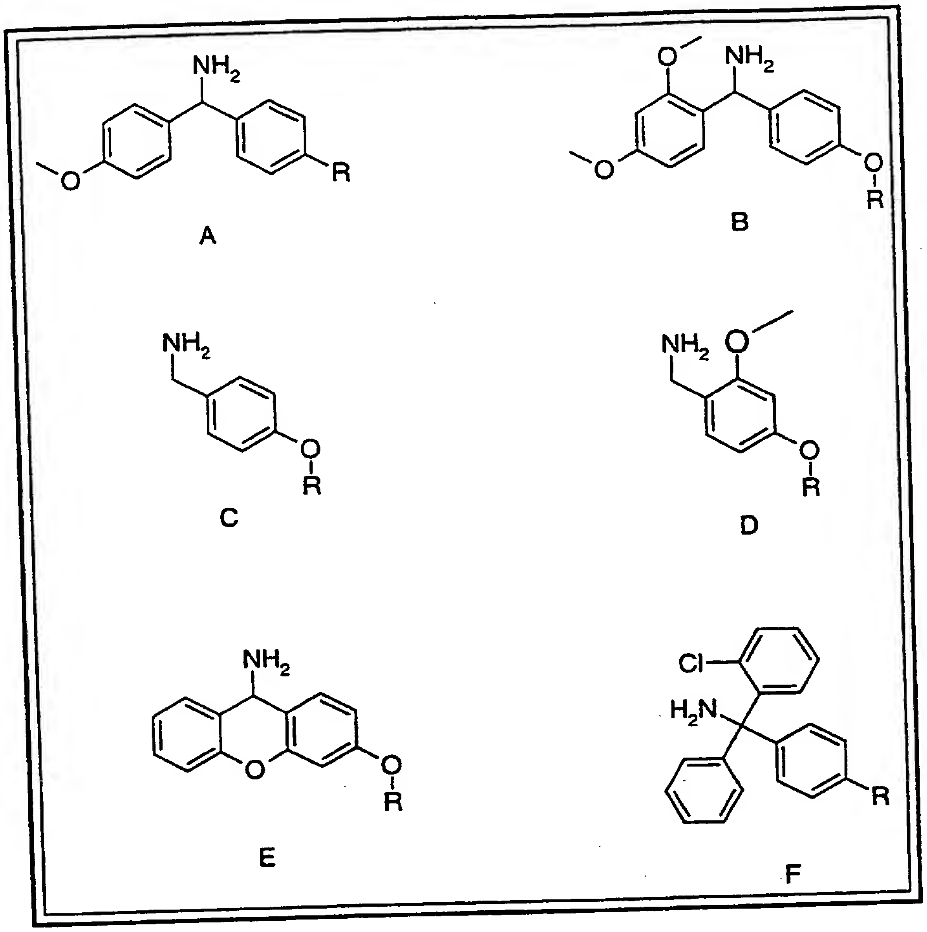


Figure 2. Linkers

In figure 2, R represents the polymeric support either directly attached to the linker or through a spacer moiety, such as a PEG-chain or a $-(CH_2)_n$-CONH- group.

Preparation of Functionalized Polymeric Reagents

A simple synthesis of a functionalized polymeric reagent is schematically shown in Figure 3 and described in more detail in Example 1.

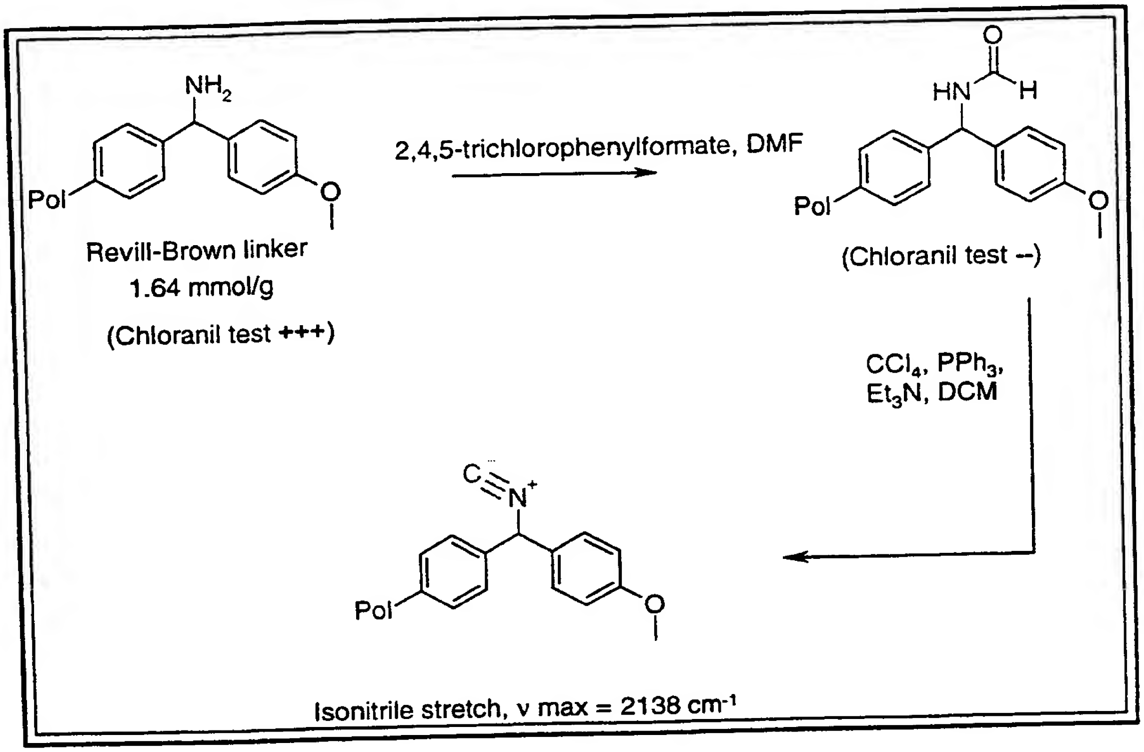


Figure 3. Synthesis of a Functionalized Polymeric Reagent

In this example, the functionalized resin is prepared by mixing a polymeric support (for example, amino MAMP linker 100-200 mesh or 200-400 mesh, commercially available from Novabiochem) in a polar solvent (*e.g.*, DMF) with a suitable "formylating" reagent, *e.g.* 2,4,5-trichlorophenylformate, as shown in figure 3. The reaction can be performed at room temperature or, in certain embodiments, at elevated temperature to ensure completeness of reaction and/or to decrease reaction times. The time required for the reaction can range from about 3 hours to 24 hours or more; an exemplary reaction time is 12 hours at room temperature.

The formed formamido intermediate is thereafter reacted at room temperature with carbon tetrachloride (CCl_4) / triphenylphosphine (PPh_3) in a non-polar solvent, *e.g.* dichloromethane (DCM) for approximately 3 hours in the presence of a base, *e.g.* triethylamine (Et_3N) to give the corresponding isonitrile.

This procedure has the advantage that is requires only a minimum number of synthetic steps, uses readily available reagents, and provides a functionalized polymeric reagent in good yield with simple purification steps.

Completeness of reaction with the functionalized polymeric reagent or polymeric supportcan be assessed according to standard techniques such as microanalysis, spectroscopic analysis, or by colorimetric tests. For example, the formation of an isonitril moiety can be monitored by Fourier-transform infra-red spectroscopy (FT-IR), e.g., by monitoring the isonitril stretch at 2138 cm^{-1}. Once the reaction has reached a pre-selected endpoint, the resin is preferably purified by washing. To ensure removal of excess reagents, several cycles of washing, preferably with solvents of a variety of polarities, can be carried out.

Once the functionalized polymeric reagent or polymeric support has been prepared and washed it is stable at room temperature for long periods of time. The functionalized polymeric reagent can be stored for extended periods of time without loss of activity.

Cleavage of Compounds from the Polymeric Support

It will be appreciated from the foregoing that the present invention provides a functionalized polymeric reagent, comprising an acid labile isonitrile moiety for use in solution and solid-phase synthesis. Compounds can be cleaved from the polymeric support with a variety of acids including, but not limited, to the following; TFA in DCM (20%), 4 M HCl in dioxane, HF, acetic acid in DCM (80%). A person skilled in the art can easily optimize the conditions to get the best possible result in the cleavage step. In general, the resin-bound compounds are preswollen in DCM for 10 min, the resin filtered and a solution of DCM:TFA:water (80:18:2) or 4M HCl in Dioxane was added and the reaction mixture was agitated for 1 hour at room temperature. The solution is filtered and evaporated to give the crude final compound.

Synthesis of Organic Compounds on the Polymeric Support

The present invention provides a method for synthesizing organic compounds by solution or solid-phase synthesis. In one embodiment, the method includes the steps of immobilizing a substrate compound on a polymeric support and at a later stage, cleaving the product from the polymeric support with an acid. As described in more detail below, in certain embodiments, the substrate compound is provided as a variegated population of substrate compounds, such that a library of organic compounds can be prepared.

Persons skilled in the art will appreciate that the immobilized substrate compound can be chemically manipulated while attached to the polymeric support. Thus, in certain embodiments, the method for synthesizing organic compounds by solution or solid-phase synthesis can include a plurality of further reaction steps, after the immobilizing step but before the cleaving step. Such synthetic manipulations include reactions, which are standard in solution and solid-phase synthesis. The reaction conditions for such manipulations will generally be selected to avoid cleavage of the substrate compound from the support, unless such concomitant cleavage is desired.

Combinatorial Chemistry on the Polymeric Support

Functionalized polymeric reagents of the present invention are suitable for use in combinatorial chemistry. Accordingly, in another aspect, the invention provides a method for the solution or solid-phase supported chemical synthesis of libraries. In one embodiment, the method comprises the step of reacting a substrate compound, which is immobilized on a polymeric support of the invention, with reagent molecules under conditions such that a library of compounds is prepared. In this embodiment, at least one of the substrate compound or the reagent molecule is provided as a variegated population thereof. It will be appreciated that the method can include the step of cleaving the library

of compounds from the polymeric support. Such a cleavage step can be concomitant with the reacting step, or, in certain embodiments, can be a separate cleavage step.

Combinatorial libraries can be screened to determine whether any members of the library have a desired activity, and, if so, to identify the active compounds. Soluble compound libraries can be screened by affinity chromatography with an appropriate receptor to isolate ligands for the receptor, followed by identification of the isolated ligands by conventional techniques (e.g., mass spectrometry, NMR, and the like). Contacting the compounds with a soluble receptor can screen immobilized compounds; preferably, the soluble receptor is conjugated to a label (e.g., fluorophores, calorimetric enzymes, radioisotopes, luminescent compounds, and the like) that can be detected to indicate ligand binding. Alternatively, immobilized compounds can be selectively released and allowed to diffuse through a membrane to interact with a receptor.

Combinatorial libraries of compounds can also be synthesized with "tags" to encode the identity of each member of the library. In general, this method features the use of inert, but readily detectable, tags that are attached to the solid support or to the compounds. When an active compound is detected (e.g., by one of the techniques described above), the identity of the compound is determined by identification of the unique accompanying tag. This tagging method permits the synthesis of large libraries of compounds that can be identified at very low levels.

A variegated population of substrate compounds can provide diversity in a combinatorial synthesis. Several methodologies have been developed to perform combinatorial chemistry. Examples of such methodologies include, but is not limited to, the mix and split technology and IRORI MiniKans.

Multicomponent Reactions on the Polymeric Support

The polymeric support of the invention is suitable for use with multicomponent reactions, but not limited to them. Multicomponent reactions have become increasing common and have been extensively reviewed see *e.g. Lutz Weber, Synlett 1999, no 3, 366-374; Kevin Short, Tetrahedron vol.53, no19, 6653-6679, 1997; Sang Kim, Tetrahedron Letters, 39 (1998) 6993-6996; Blacburn. Tetrahedron Letters (1998) 39, 5469-5472, Bienayme , Angew. Chem. Int. Ed. (1998) 37, no 16; Blackburn 39, (1998) 3635-3638 Tetrahedron Letters.*

In a multicomponent reaction three or more component molecules can react simultaneously or close to simultaneously with each other to provide a molecule which has incorporated substantial portions of these reagent molecule without any isolation of intermediates. This includes reactions involving at least three different functional groups, some of which may be parts of the same reagent molecule. In general a multicomponent reaction is sequences of bimolecular reaction steps that proceed according to the zipper principle, *i.e.* each reaction step is a prerequisite for the following step. Examples of multicomponent reactions include but are not limited to, α-aminoalkylation (Mannich), Passeriini, Ugi and Ugi-type. Ugi and Ugi-type reactions are preferred multicomponent reactions to be used with the polymeric supports of the present invention. Ugi and Ugi-type reactions give access to compounds and functionalities of great interest for a medicinal chemist, *e.g.* heterocyclic compounds.

Accordingly, in another aspect, the invention provides methods for the multicomponent synthesis of organic compounds. In one embodiment, the method comprises the step of reacting the isonitrile moiety with at least two reagent molecules simultaneously under conditions such that a multicomponent reaction is achieved.

A preferred embodiment of the present invention is schematically shown below in Figure 4.

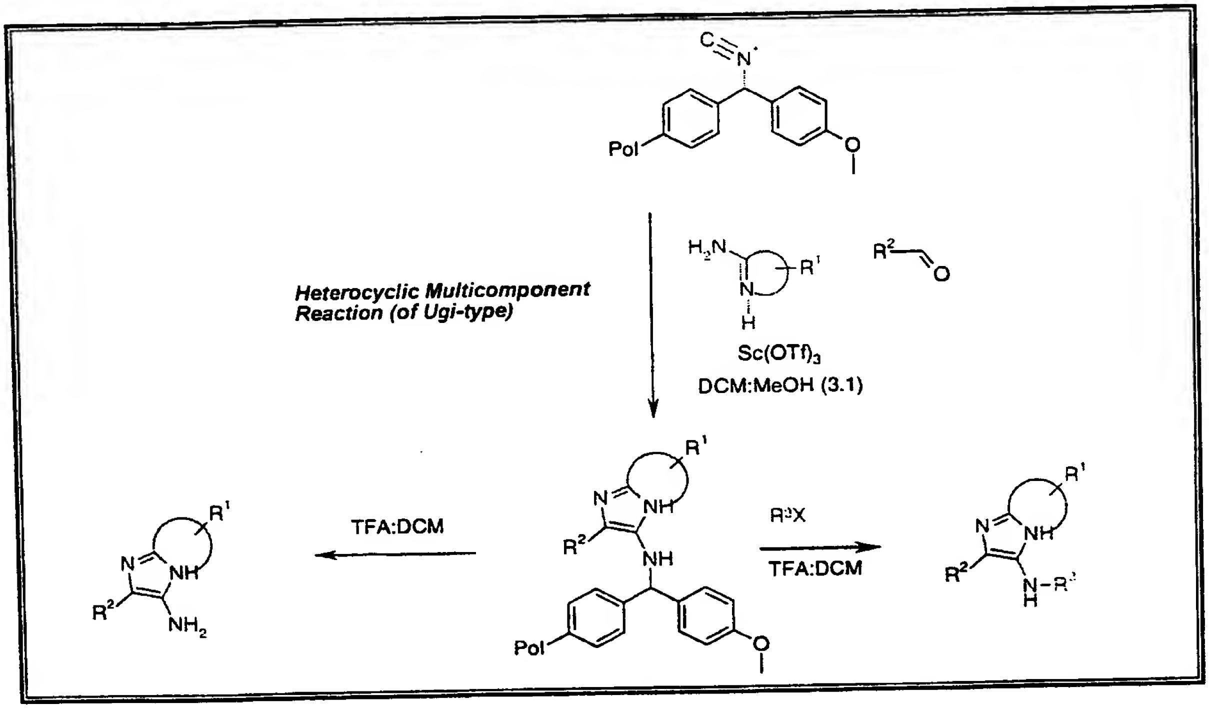


Figure 4. Heterocyclic Multicomponent Reaction

The preferred embodiment shown in Figure 4 is advantageous since it allows a multicomponent reaction to be performed directly onto the acid labile isonitrile moiety of the functionalized polymeric reagent.

The example outlined above consists of a multicomponent Ugi-type condensation wherein the isonitrile moiety of the functionalized polymeric reagent is reacted with 2 different source of diversity, aldehydes and heteroaromatic amidines. This Ugi-type reaction leads efficiently and in a one step process to the fused 3-aminoimidazoles, using the resin capture strategy. The final compounds are of high purity after acid cleavage.

3-aminoimidazoles has been synthesized according to the present invention. A wide range of aldehydes and heteroaromatic amidines was utilised to test the functionalized polymeric reagent and showed the efficiency of the resin capture by obtaining a high yield and excellent purity of the final products. Typical procedure for the synthesis of fused 3-aminoimidazoles by Ugi type reaction and resin capture strategy is described in Example 3, below.

The fused 3-aminoimidazoles contains a nitrogen atom, involved in an amine bond with the polymeric support, which can be further reacted with various electrophilic molecules, *e.g.* acyl halides, alkyl halides, or sulfonyl halides, and thereafter, be cleaved from the polymeric support. This tandem reaction process (MCR + acylation/alkylation) increases the diversity which can be introduced onto the 3-fused aminoimidazole core. The thereby introduced additional diversity is a further advantage of the present invention, since the access of these compounds by traditional solution-phase without polymeric support is cumbersome, since the corresponding isonitriles are either not commercially available or time-consuming to synthesize. Due to the low number of commercially available isonitriles able to be utilised in combinatorial chemistry (<20) and the cost and time-consumption of custom syntheses, the isonitriles have always been the poorest source of diversity involves in the Ugi reaction.

One of the advantages of the present invention is to overcome this kind of problem. The amino functionality of the aminoimidazoles can be utilised for further reactions, such as acylation or alkylation reactions. For example, acyl chlorides, sulfonyl chlorides or alkyl halides can be used as source of diversity and will enhance the diversity of the aminoimidazoles. The Tandem reaction concept by coupling a multi component reaction with an additional alkylation or acylation step makes the whole process highly efficient with respect to the final diversity of the aminoimidazoles synthesized. The present invention also have a postitive impact on the size and the speed by which a library can be generated. The tandem 3CC+1 strategy has enhanced the diversity of the fused 3-aminoimidazoles by using 3 non-exhaustive sources of diversity, *i.e.* acyl chlorides, alkyl halides and sulfonyl chlorides. The typical procedures for the synthesis of these compounds are described below in Example 3.

The polymeric support of the present invention can also be used in general organic chemistry manipulations, such as cycloaddition reactions, as a dehydrating agent or as a

scavenger, *e.g.* for the removal of alkyl halides, phosphines, acid chlorides, aldehydes and ketones.

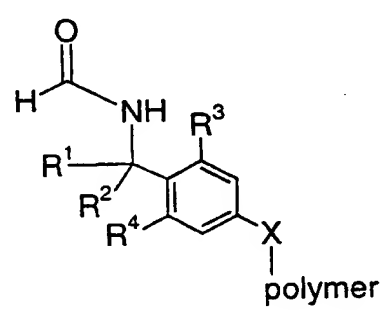
Kits

The present invention also provides a kit for use in solution and solid-phase synthesis. The kit includes a functionalized polymeric reagent of the present invention, *i.e.* for use in solution and solid phase chemistry, preferably in a container or package.

Intermediates

It is an object of the present invention to provide new intermediates for use in the preparation of the novel functionalized polymeric reagents.

Useful intermediates according to the present invention are compounds of Formula II



(II)

wherein

X is carbon, oxygen, a PEG-chain, or a $-(CH_2)_n$-CONH- group

R^1 is hydrogen, phenyl, or substituted phenyl group,

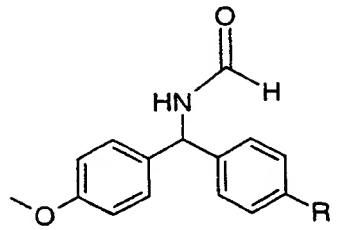
R^2 is hydrogen, phenyl, or substituted phenyl group,

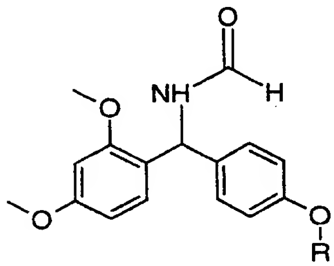
R^3 is hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or phenoxy,

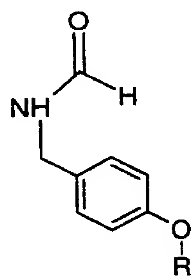
R^4 is hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy, or phenoxy, and

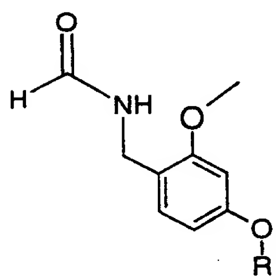
n is an integer from 1 to 4.

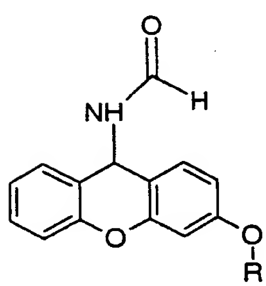
Preferred intermediates of the present invention are the following compounds;

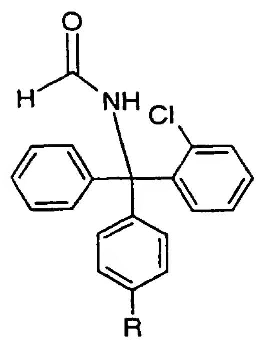












wherein, R represents the polymeric support either directly attached to the linker or through a spacer moiety, such as a PEG-chain or a $-(CH_2)_n$-CONH- group.

EXAMPLES

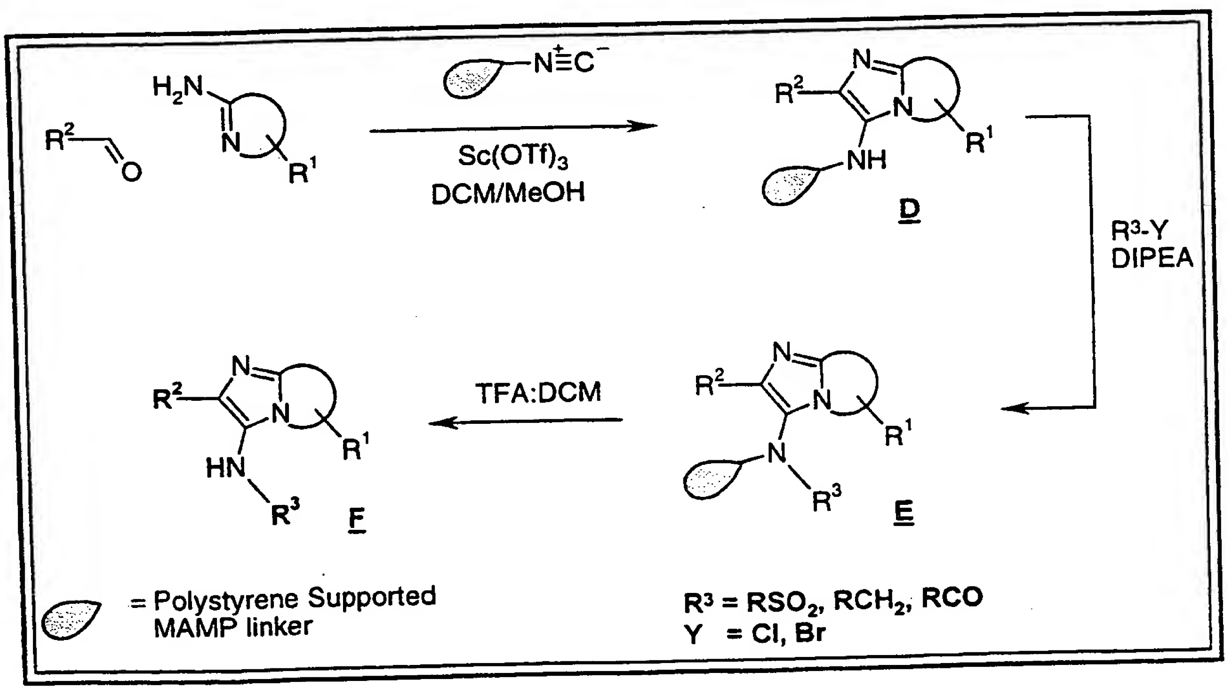
Example 1. Preparation of Functionalized Polymeric Reagent

The starting MAMP amino resin (1 gr; 1.64mmol/g) was pre-swollen in DMF for 10 minutes. To this resin was added a solution of 2,4,5-trichlorophenyl formate (560mg; 2.46mmol, 1.5eq) in 10 mL of DMF. The reaction mixture was agitated at room temperature for 12h. The resin was filtered and washed with DMF (2x10mL), DCM (2x10mL), MeOH (2x10mL) and finally dry under vacuum for 1 hour. The resin gives a negative chloranil test, which indicates completion of the reaction. The resin (1.64mmol) was thereafter washed with dry dichloromethane (2x10mL), pre-swollen in dry dichloromethane for 10 min, and filtered. A solution of triphenylphosphine (2.16g, 8.2mmol, 5eq), carbon tetrachloride (1.27g, 8.2mmol, 5eq) and triethylamine (830mg, 8.2mmol, 5eq) in dry dichloromethane 10mL was added followed by a few activated molecular sieves (4Å). The reaction mixture was shaken at room temperature for 3 hours. The resin was filtered, and washed with dichloromethane (2x10mL), methanol (2x10mL), and dichloromethane was added to afford the separation of the floating resin from the molecular sieves. The resin was washed with 10mL dichloromethane and diethyl ether

(2x10mL) and dried under vacuum for 12h. The resin was then kept under nitrogen at room temperature in the dark for 6 months without any modifcation of its efficiency.

Example 2. Resin Capture Strategy for the synthesis of fused 3-amino imidazoles.

The heteroaromatic amidine (323μmol, 200mol%), the aldehyde (323μmol, 200mol%) and the catalyst $Sc(OTf)_3$ (16.2μmol, 10mol%) in 1mL of a solution of DCM:MeOH (3:1) were incubated for 30min. The resin isonitrile linker (100mg, 163μmol, 100mol%) was preswollen for 20 minutes in DCM and the resin filtered. The solution of aldehyde, heteroaromatic amidines and catalyst was then added to the resin and the solution was shaken for 2 days at room temperature. The resin filtered and washed with DCM(2x3mL), MeOH(2x3mL), 20%DIPEA in DCM(3mL) and DCM(2x3mL). A sample of the resin (3-5mg) was cleaved from the resin with a solution DCM:4M HCl in dioxane(1:1) for 1h at room temperature. The residue was dried under vacuo and analysed by LC-MS, yielding the expected product in high purity (75-99%).



Scheme 1. Enhancement of diversity by reacting the nitrogen atom, involved in an amine bond with the polymeric support, *of the fused 3-aminoimidazole with various electrophiles.*

Exemple 3. Synthesis of amide substituted fused 3-aminoimidazoles

Resin-bound compound **D** (60mg, 74μmol, 100mol%) was preswollen in DCM for 20 minutes and the resin filtered. A solution of acyl chloride (370μmol, 500mol%) and DIPEA (600μmol, 800mol%) in 1mL of DCM was added to the resin-bound compound **D** and the reaction mixture was agitated for 20h at room temperature. The resin was filtered and washed with DCM (2x3mL), MeOH (2x3mL), and DCM(2x3mL). A sample of the resin (3-5mg) was cleaved from the resin with a solution of DCM:TFA:water (80:18:2) for 1h at room temperature. The residue was dried under vacuo and analysed by LC-MS, yielding the expected product in high purity (75-99%).

Exemple 4. Synthesis of alkylated 3-aminoimidazoles.

Resin-bound compound **D** (60mg, 74μmol, 100mol%) was preswollen in DMF for 20 minutes and the resin filtered. A solution of alkyl halides (370μmol, 500mol%) and DIPEA (740μmol, 1000mol%) in 1.2mL of DMF was added to the resin-bound compound **D** and the reaction mixture was agitated for 20h at 80°C. The resin was filtered and washed with DMF (2x3mL), DCM (2x3mL), MeOH (2x3mL), and DCM(2x3mL). A sample of the resin (3-5mg) was cleaved from the resin with a solution of DCM:TFA:water (80:18:2) for 1h at room temperature. The residue was dried under vacuo and analysed by LC-MS, yielding the expected product in high purity (75-99%).

Exemple 5. Synthesis of sulfonamide substituted 3-aminoimidazoles.

Resin-bound compound **D** (60mg, 74μmol, 100mol%) was preswollen in DCM for 20 minutes and the resin filtered. A solution of sulfonyl chlorides (370μmol, 500mol%) and DIPEA (740μmol, 1000mol%) in 1.2mL of DCM:Dioxane (1:1) was added to the resin-

bound compound **D** and the reaction mixture was agitated for 20h at 60°C. The resin was filtered and washed with DCM (2x3mL), Dioxane (2x3mL), MeOH (2x3mL), and DCM(2x3mL). A sample of the resin (3-5mg) was cleaved from the resin with a solution of DCM:TFA:water (80:18:2) for 1h at room temperature. The residue was dried under vacuo and analysed by LC-MS, yielding the expected product in high purity.